REMARKS

Claims 1-6 and 8-12 were previously amended. Claims 1-6 and 8-12 now stand rejected. Claim 9 is presently amended to more clearly set forth the order of method steps in preparing the combined immunogenic composition. Applicant respectfully requests reconsideration of the application in view of the following remarks.

Rejection under 35 U.S.C. § 102(b)

Claims 1-6 and 8-12 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Dalemans, et al. (WO 99/30733).

The Office Action states that Dalemans, et al. teach combination vaccines comprising nucleic acid and a polypeptide in combination with adjuvants, that Dalemans, et al. teach the prior mixing of the polypeptide or protein antigen with the adjuvant and a method of use in a combined DNA/ protein vaccine composition.

Applicants respectfully assert that, claim 9 either as previously presented or as currently amended does not include a "wherein" clause. Rather claim 9 (as now amended) recites "preincubating or subsequently mixing the mineral-based, negatively charged adjuvant with said at least one protein antigen immunogenic component; and adding said polynucleotide immunogenic component to the adjuvant protein mixture to form the combined immunogenic composition". Accordingly, claim 9 specifies the order of the mixing which must be considered for a determination of patentability.

Furthermore, claim 1 has been amended to include these process steps. Specifically, claim 1 has been amended to recite "said composition produced by a method comprising preincubating or subsequently mixing said mineral-based negatively charged adjuvant with said at least one protein antigen immunogenic component prior to formulating with said polynucleotide immunogenic component". Accordingly, the order of mixing the mineral-based negatively charged adjuvant with the protein antigen immunogenic component and formulation with the polynucleotide immunogenic component is now set forth in claim 1.

As set forth in M.P.E.P. section 2113,

> The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is

made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.

In the present case, the process steps describe a structural difference with respect to the cited prior art reference which can only be defined by the process steps as recited in amended claim 1. In this regard, Applicants point out that the order of mixing clearly changes the outcome. For instance, if [A] can bind to either [B] or [C], a prior mixing of [A] + [B], with a subsequent addition of [C] gives [A,B] + [C], a prior mixing of [A] + [C], with a subsequent addition of [B] gives [A,C] + [B]. Clearly, the order of mixing provides a different end-result although the initially used components are identical.

Applicants emphasize that the order of mixing the components of the composition results in a structure in toto which differs from the structures of the compositions which were made by a different order of mixing the components. The different structure is exemplified by a different effect, *inter alia* a significantly enhanced immunogenicity of the polynucleotide component, compared to another order of admixing the components or the omission of the adjuvant. This is extensively described in the application and corroborated by the examples. The eventual product is characterized by the process by which it is made.

The immunogenic composition of the invention was not known

As discussed above, the claims have been amended to clearly specify the order of mixing of components. The specific order of mixing, which was neither disclosed nor suggested in Dalemans, et al., is important for achieving a specific end-result. This specific end-result was neither disclosed nor suggested in the prior art, i.e. the immunogenic composition of the present invention provides effects different from known vaccine compositions. Accordingly, the immunogenic compositions of the presently claimed invention are not anticipated by Dalemans, et al..

Dalemans does not teach the order of mixing as presently claimed

Dalemans, et al. do not teach or suggest "said composition produced by a method comprising preincubating or subsequently mixing said mineral-based negatively charged adjuvant with said at least one protein antigen immunogenic component prior to formulating with said polynucleotide immunogenic component" as now claimed (claim 1 as amended). In fact, Dalemans, et al. teach administrating of the DNA and protein in the "vaccine" at the same time

(see Dalemans, et al., page 3, line 30; page 4, lines 6-8; page 7, line 15; and claim 22). One of ordinary skill in the art, based upon the disclosure of Dalemans, et al., would administer the DNA and protein simultaneously, as taught by Dalemans, et al. and there is no teaching on admixing the compounds in any specific order. Dalemans does not provide any order of mixing the components, let alone preincubating or mixing said mineral-based negatively charged adjuvant with a protein antigen vaccine component prior to formulating with a polynucleotide vaccine component as required by the present invention. Accordingly, this feature of the invention is neither taught nor suggested by Dalemans, et al.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Dalemans does not teach the use of adjuvants as presently claimed

Dalemans, et al. teach away from the claimed invention in teaching that the use of immunostimulants (adjuvants) may be obviated. See page 5, first paragraph of Dalemans, et al. which is reproduced below:

> Another benefit of the present invention is that in certain cases, where there is a predisposition to a strong immune response (e. g., high percentage of responders to initial vaccination, high level of antibody titers, CTL response, etc.), the combination of both compounds (DNA + protein) can obviate the need for immunostimulants.

Furthermore, the suggestion of Dalemans, et al. in the section reproduced above to use vehicles which do not bias the immune response would also be viewed by one of ordinary skill in the art to teach away from the claimed invention as mineral adjuvants bias the immune response towards Th-2.

Dalemans, et al. is silent regarding the effects of the different adjuvants and the importance of electric charge. Dalemans merely provides a very general list on adjuvants without specifying a preference for mineral-based negatively charged adjuvants, and including adjuvants which do not work. Dalemans, et al. teach that it is preferable not to use an adjuvant at all.

Accordingly, based upon Dalemans, et al., one of ordinary skill in the art would not use an adjuvant at all, contrary to the claimed invention.

Dalemans, et al. do not provide an enabling disclosure

Referring to the points raised in the scope of enablement rejection of the Examiner's Final Office Action, Applicants point out that these same points are pertinent to the disclosure of Dalemans, et al.

For example,

- Dalemans does not demonstrate any in vivo protective immunity (cf. Boslego et al.).
- Dalemans does not provide challenge experiments.
- Dalemans provides no teaching of the most effective route of administration (cf. Ellis).
- Dalemans contemplates that correct folding of the protein is achieved when said protein is encoded by a gene via intracellular expression (Dalemans, et al. page 7, lines 1-7).
- Dalemans connotes delayed response of the protein component (thus without an adjuvant).
- Dalemans requires that the epitope encoded by the polynucleotide is identical to the epitope of the polypeptide. On page 4, lines 19-21 it is stated that "This enhancement is specific to the polynucleotide added, as a similar polynucleotide not encoding the specific polypeptide was unable to enhance the immune responses." Example 6 demonstrates the same. All experiments are performed with the same epitope on both the polypeptide and the polynucleotide (Note that R5V-G has not been tested).
- The synergistic effect of Dalemans is not conclusive, since different amounts of polypeptide and/or polynucleotide are used in the different experiments, including the control experiments.
- In the Dalemans experiments, only antibody titers are increased, relative to the "control" experiments (see Figure 1).
- Dalemans provides no conclusive results regarding the cellular response of the various combinations, i.e. proliferation vs. IL-S vs. IFNy vs. CfL responses (see Table 1).

Accordingly, Dalemans, et al. do not provide an enabling disclosure.

Summary

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this

application that previously pending claims in any jurisdiction are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application. Any amendments made by way of the present paper, and the observations contained herein, are made solely for the purposes of the prosecution of this U.S. Patent application and without prejudice to the Applicant in other jurisdictions.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: 9/22/08

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